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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/124,485	07/29/1998	NICHOLAS MARK ANSTEY	73-97	6763

7590 07/16/2002

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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 07/16/2002 18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/124,485	Applicant(s) ANSTEY ET AL.	
	Examiner Gailene R. Gabel	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2002 and 07 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-33 and 38-45* is/are pending in the application.

4a) Of the above claim(s) *27-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *27-33 and 38-45* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/14/02 in Paper No. 13 and 5/7/02 in Paper No. 17 have been entered. Claims 1-26 and 34-37 have been cancelled. Claims 38-45 have been added. Claims 38 and 41 have subsequently been amended. Accordingly, claims 27-33 and 38-45 are pending. Claims 38-45 are under examination.

Withdrawn Rejections

2. The rejections of claims 1-26 and 34-37 are now moot in light of Applicant's cancellation of the claims.

New Grounds of Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 38-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 is indefinite in reciting, "NO". Acronyms or abbreviations must be fully defined and recited at least one time in a set of claims.

Claim 38 is vague and indefinite because it is unclear what Applicant intends to encompass in reciting, "modifying", i.e. increasing, decreasing, etc.

Claim 40 lacks antecedent support in reciting, "the protozoa".

Claim 41 is incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. Specifically, it is unclear how NO relates structurally or functionally, to the "NO modifying agent" in claim 38 from which it depends. It is unclear how NO in itself is a modifying agent for NO, by failing to specifically define how the "agent" is an NO. Applicant is reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim 42 is vague, indefinite, and incomplete as depending from claim 38, for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. Specifically, it is unclear how an NO donor which is an NO modifying agent, is administered by inhalation, because while "NO" itself is in gaseous form, the "agent"

itself has not been clearly and distinctly defined as being in gaseous form which can be inhaled, for administration. Please clarify.

Regarding claim 43, the phrase "and/or" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "and/or"), thereby rendering the scope of the claim unascertainable.

Regarding claim 43, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 44 has lacks antecedent support in reciting, "the corresponding thiol".

Claim 45 is vague and indefinite in reciting, "the NO modifying agent includes" because it is unclear what other elements are "included" with the NO modifying agent.

Claim 45 is indefinite in reciting overlapping Markush groups.

Claim 45 is indefinite in using parenthetical symbols because it is unclear whether the limitations within the parentheses are a part of the claimed invention.

Regarding claim 45, "e.g." renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 38-39, 42-43, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seguin et al. (The Journal of Experimental Medicine, 1994) in view of Green et al. (US 5,814,666).

Seguin et al. teach the importance of NO modifying agents, i.e. L-arginine, CD8 T-cells and interferon (IFN-γ) as NO donors, in the regulation of induced nitric oxide synthase (iNOS), in liver stage malaria wherein cells are exposed to sporozoites (liver stage) of Plasmodium berghei. NO donors contribute to the protective response of mice immunized with irradiated Plasmodium. To determine the participation of NO to protective response to malaria, L-arginine analogues were orally administered (gastric instillation) to immunized mice before sporozoite challenge and found that substrate inhibitors for NOS suppress NO synthesis and NO-mediated events in vivo and in vitro (see page 355, column 1). While immunity in Seguin's study is directed against liver stage malaria, another publication (Taylor-Robinson et al.), reported that induction of

NO by T_h1 CD4 cells controls blood stage malaria. Specifically, Seguin et al. teach that NO donors kill parasites by stimulating or inducing production of NO for the destruction of hepatocytes and parasites within the cells in both mice and humans (see Abstract).

Sequin et al. differ from the instant invention in failing to administer NO modifying agents via inhalation.

Green et al. disclose a method of treating parasitic infection caused by pathogenic microbes, i.e. Leishmania, in humans and other mammals, by administering via inhalation, a nitric oxide (NO) modifying agent (NO releasing compound or NO generators) that is encapsulated in vesicles such as liposomes (see column 4, lines 31-42 and column 5, lines 3-9). The NO modifying agent is released to induce cytostasis or cytotoxicity amongst cells exposed to the parasite and to kill, inhibit, and retard growth or infectivity of the parasite (see column 4, lines 43-67). Green et al. provides a list of NO modifying agents, i.e. spermine-bis(NO) adduct monohydrate and 3(n-propylamino)propylamine bis(NO) adduct, in columns 6-8 and 13, especially lines 5-51, and Table 1. Alternatively, Green et al. teach that NO modification may be done by forming NO gas metabolically from the amino acid L-arginine through the action of the enzyme nitric oxide synthase (see column 3, lines 20-27). Formulations of the NO modifying agent are provided for oral administration as well as for inhalation, i.e. aerosol formulations (see column 12, especially lines 32-37).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Green in administering by inhalation, NO modifying agents that release NO, into the method of Seguin that orally administers NO

to induce NO production to kill intracellular Plasmodium species, because Green specifically taught that directed delivery of NO into Leishmania infected macrophages, kills the intracellular pathogen during blood stage of the parasite and an ability to specifically deliver NO releasing agents to desired sites of infection, i.e. peripheral blood cells, would greatly enhance killing of these intracellular parasites.

5. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seguin et al. (The Journal of Experimental Medicine, 1994) in view of Green et al. (US 5,814,666) as applied to claims 38-39, 42-43, and 45 above, and further in view of Kremsner et al. (Transactions of the Royal Society of Tropical Medicine and Hygiene, 1996).

Sequin et al. and Green et al. have been discussed supra. Seguin et al. and Green et al. differ from the instant invention in failing to disclose that the Plasmodium species causing parasitic infectivity is P. falciparum.

Kremsner et al. teach that high plasma levels of NO in acute phase of Plasmodium falciparum malaria predicts accelerated cure which provides evidence of the protective role of NO in malaria (see Abstract). Kremsner et al. teach that the production of NO is induced by cytokines as shown in vitro with murine macrophages, in vivo in dogs and in vitro with human cells. Kremsner et al. teach that high plasma levels of NO have previously been reported in P. falciparum and P. vivax and that NO has been shown to be toxic in vitro for P. falciparum (see page 44). In their study, Kremsner et al. measured nitrite and stable products of NO, in plasma of semi-immune patients

and found that upon admission, NO correlated with parasitemia and was significantly higher in patients with severe malaria than in patients with uncomplicated malaria (see page 46, column 1). Alternatively, in another publication (Camerron et al.) the duration of coma in cerebral malaria has been shown to be inversely correlated with NO plasma levels which provides evidence that excessive production of NO may also be deleterious. However, Kremsner et al. teach that NO produced within the network of a **directed immune response** plays a key protective role against malaria infection.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the NO modifying agents via inhalation in the method taught by Seguin as modified by Green, to patients infected with P. falciparum and undergoing NO treatment as in the teaching of Kremsner, because Kremsner specifically taught that NO plays a protective role in the treatment of malarial infection by P. falciparum and both Seguin and Green are generic with the type of intracellular blood stage parasite upon which NO treatment is applied for treatment, and P. falciparum appears to be an obvious variation of the Plasmodium species known to infect blood intracellularly.

6. Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seguin et al. (The Journal of Experimental Medicine, 1994) in view of Green et al. (US 5,814,666) as applied to claims 38-39, 42-43, and 45 above, and further in view of Stamler et al. (Proc. Natl. Acad. Sci. USA, 1992).

Sequin et al. and Green et al. have been discussed supra. Green et al. and Seguin et al. differ from the instant invention in failing to disclose that the NO donor results in the formation of R-S-NO compound wherein the R-S moiety is derived from the corresponding thiol, R-SH.

Stamler et al. teach that naturally produced NO circulates in the plasma primarily complexed in S-nitrosothiol species (see Abstract). Stamler et al. also specifically teach that pharmacological interventions that modulate NO generation changes plasma levels of S-nitrosothiols. The abundance of nitrosothiols in plasma compared with free NO suggests that plasma S-nitrosothiols serve as reservoir for NO to effectively buffer its concentration (see page 7677). Table 1 lists plasma levels of NO and nitrosothiols in humans. Additionally, Stamler et al. teach that NO reacts in the presence of specific protein thiols to form S-nitrosoprotein derivatives. Human plasma contains 7μm nitrosothiols of which 96% are S-nitrosoproteins, 82% of which is accounted for by nitroso-serum albumin. Stamler et al. teach that administration of monomethyl-L-arginine which is a selective and potent inhibitor for NO synthase decreases nitrosothiol by 40%.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the teaching of Stamler into the method taught by Seguin as modified by Green, because both Seguin and Green provide methods of modifying NO levels in order to treat parasitic infections and that there is a prophylactic effect of increased NO levels in the treatment of Leishmania and Plasmodium species in infected macrophages, by killing the intracellular pathogen during blood stage of the

parasite and therefore, an ability to specifically deliver NO releasing agents to desired sites of infection, i.e. peripheral blood cells, for complexation into S-nitrosothiol, would greatly enhance killing of these intracellular parasites, given the teaching that nitric oxide should exist in the plasma naturally as being primarily complexed in S-nitrosothiol because S-nitrosothiols serve as reservoir for NO.

Response to Arguments

7. Applicant's arguments with respect to claims 38-40 and 42-45 have been considered but are moot in view of the new grounds of rejection.

Allowable subject matter

8. Claim 41 may be allowable if rewritten to overcome the rejection under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. Prior art of record fails to teach or fairly suggest a method of treating parasitic infection by Plasmodium species by administering via inhalation, nitric oxide gas.

Remarks

9. Prior art made of record are not relied upon but considered pertinent to the applicants' disclosure:

Radhakrishnan et al. (US 4,895,719) disclose a method of administering a drug at a selected dose via inhalation through the respiratory tract. Specifically,

Radhakrishnan et al. disclose using spray-dried liposome particles containing therein a selected dose of the entrapped drug for release in aerosolized form (see Abstract). According to Radhakrishnan et al., inhalation route allows a drug to be rapidly delivered to the bloodstream and is suitable for drugs which cannot be delivered orally because of drug stability, i.e. unstable in free form (see columns 15-16).

Losert et al. (Intensive Care Medicine, February 2000 –not prior art) teach treating malarial patients infected by Plasmodium falciparum with inhaled nitric oxide as anti-malarial treatment.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday-Thursday from 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel

Patent Examiner
Art Unit 1641

7/13/02

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641